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*Review*

# Factors influencing the gut microbiome in children: from infancy to childhood

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The human microbiota plays a crucial role in educating the immune system and influencing host health right since birth. Various maternal factors along with the vertical microbial transfer from the mother, as well as the horizontal environmental transmission and internal factors relating to the infant, play a crucial role in modulating the gut microbiota. The early life microflora is highly unstable and undergoes dynamic changes during the first few years, converging towards a more stabilized adult microbiota by co-evolving with the host by the age of 3–4 years. Microbiota studies have underlined the role of dysbiosis in developing several metabolic disorders like obesity, diabetes and immune-related disorders like asthma, to name a few. Thus, understanding early life microbial composition and various factors affecting the microbial community will provide a platform for developing strategies/techniques to maintain host health by restoring gut microbial flora. This review focuses on the factors that affect the microbial composition of the foetus *in utero*, during birth, infancy through childhood.

**Keywords.** Birth mode; infants; maternal health; microbiome

## 1. Introduction

The study of the human gut microbiome has gained importance in past years due to the important contribution of microbes in host health, stimulating immune system development, host nutrient metabolism, as well as promoting differentiation of mucosal structure and function. These actions of the microbiota have a widespread impact beyond the gastrointestinal tract (Tremaroli 2012; Doré *et al.* 2013; Cénit *et al.* 2014). The gastrointestinal tract (GIT) is known to be the most densely populated anatomical site forming a 'mini-ecosystem' (Tojo *et al.* 2014). Thus, characterizing the gut microbiota is one of the most important aspects of understanding the host microbiome relation. The flexibility of the human gut microbiome is a characteristic feature as, despite the daily oral intake of particular food, the composition of the microbiota and the metagenome remains essentially unaffected. Influences on the microbiota are evident across the human lifespan and depend on various internal and external factors (Ottman *et al.* 2012; Odamaki *et al.* 2016; Korpela and de Vos 2018).

Post birth, the composition of the microbiota is initially derived from colonization by the early settlers to which a baby is exposed in their environment, and during delivery, which, along with other factors, such as diet and medications, substantially affect the entry of subsequent microbial species into the suitable micro-environments in the host. Before birth, the foetus is highly protected and isolated by the mother with everything being filtered by the mother's organs before reaching the baby *in utero* (Perez-Muñoz *et al.* 2017). At birth, the immune system of a foetus is thus not well educated, which is partially beneficial as the foetus

cannot mount a severe reaction against the maternal antigens (Yan *et al.* 2004; Al-Hertani *et al.* 2007; Gervassi and Horton 2014). Studies suggest that the GIT microbiota acts as a major source of antigens including peptidoglycan, lipoproteins, lipopolysaccharides and flagellin. All of these antigens shape, activate and educate the innate and adaptive immune systems (Schwandner *et al.* 1999; Wang *et al.* 2001; Patten and Collett 2013). Thus, an individual requires a stable microbial composition (microscopic composition), along with a suitable macro environment (as the bodily/surrounding environment affects the microbial diversity), for normal metabolic functioning of the microbiota.

While a dysbiotic microbial composition can disturb the biological functions in the host, a healthy microbial community is needed for maintaining sound health. The interaction between the microbiome and host is most crucial during the early lifetime as critical changes in the abundance and composition of the microbiome prevail in early life, which becomes more or less stable and remains throughout a lifetime, thus dictating the health of future adult life (Neu 2015). During the early years of life, the intestinal microbiome is relatively dynamic, and these initial dwellers have a key impact on the host health throughout life (Scholtens *et al.* 2012; Tanaka and Nakayama 2017). Thus, it is important to understand the factors that influence and modify the microbiome at various stages of life for an individual, with an emphasis on early life. This review focuses on the various factors that affect the microbiota of children from infancy to childhood.

## 2. Phase 1: Foetal stage

### 2.1 *Maternal diet during pregnancy*

The bacterial colonization of the neonatal gut begins when *in utero* and the maternal intestinal flora is a major source of healthy microbiota for the infant, which persists during the early weeks of life (Vaishampayan *et al.* 2010). Gut microbial composition varies with the diet and health status of the host, and these factors during pregnancy can affect the maternal gut microbiota, which in turn can affect the infant *in utero* and even post birth (figure 1). Previous studies have not only shown a clear association between diet and gut

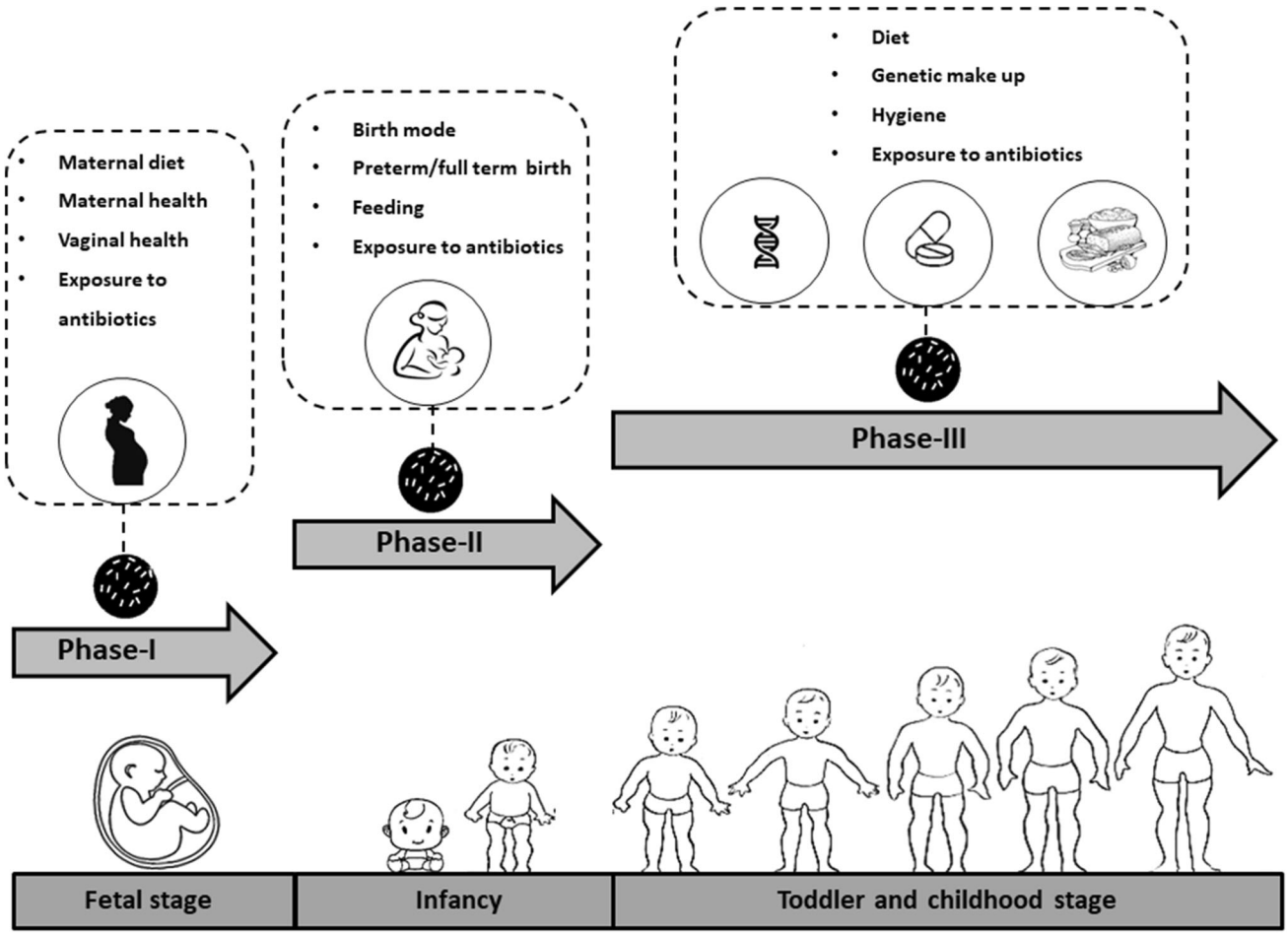


**Figure 1.** Overview of the factors influencing the gut microbiome at different stages from phases 1 to 3 (foetal stage, infancy, toddler and childhood stage).

microbiome but have effectively proved the importance of maternal dietary modulations in influencing the changes in the gut microbiome (Chu *et al.* 2016; Lundgren *et al.* 2018).

Recently, Kristen Meyer *et al.* using two dietary treatments in a longitudinal study reported that modifying the maternal diet (like changing fat to carbohydrate intake or changing consumption of specific sugars) is associated with significant alterations in the milk microbial composition and human milk oligosaccharide (HMO) composition (Meyer *et al.* 2017). The breast milk microbiome and HMOs come in direct contact with the breastfeeding infants and thus can modify their gut microbial composition (Jost *et al.* 2015). The results thus suggest a possible role of maternal food habits during and post pregnancy on infant gut microflora development (Meyer *et al.* 2017).

In another study in mice, Gohir *et al.* (2015) looked into how the maternal diet (before and during pregnancy) affects the gut microbial composition. In case of high-fat fed female mice, the authors observed significant changes in the gut microbiota composition later in pregnancy, compared to those fed on a normal chow diet. Mothers fed with a high-fat diet before and during pregnancy had higher levels of *Akkermansia* and *Bifidobacterium*. These changes in the microbial composition can alter the abundance of genes that favour various metabolic processes during pregnancy (Gohir *et al.* 2015) and thus can affect the inceptive microbial composition of the infant. Further, Gibson *et al.* demonstrated that exposure to specific food items, such as fish oil (PUFA rich diet) to rat dams, resulted in a decrease in microbial richness and altered intestinal microbial composition (Gibson *et al.* 2015). The authors also observed that offspring born to mothers consuming fish oil showed an abundance of taxa of opportunistic pathogens like *Bilophila wadsworthia*, *Enterococcus faecium* and *Bacteroides fragilis* in their gut which can lead to altered immune response (Gibson *et al.* 2015). Also, studies have shown that risks for spontaneous preterm delivery (Myhre *et al.* 2011) and childhood allergic diseases (Bertelsen *et al.* 2014) are reduced by habitual maternal intake of probiotic-containing food.

A recent study in *Macaca fuscata*, a primate model, revealed that maternal consumption of high-fat diet during pregnancy or post birth results in dysbiosis of the neonatal intestinal microbiome (Ma *et al.* 2014). They observed the dominance of *Bacteroidetes* and the absence of *Spirochetes* in the gut of high-fat diet fed dams. These shifts were accompanied by a decrease of *Treponema* and increased the abundance of *Prevotella* (Ma *et al.* 2014). Similar to the results obtained in primate studies, Chu *et al.* (2016) demonstrated that in humans too, a high-fat maternal diet alters the neonatal gut microbiome independent of the maternal body mass index. They observed that the infant gut microbial composition varied by maternal diet during pregnancy with *Bacteroides* levels reduced in infants born to mothers consuming a high-fat diet during pregnancy (Chu *et al.* 2016). Another less studied factor is alcohol consumption during pregnancy and its ill effects on faecal microbiome development. Alcohol consumption during pregnancy has been associated with various disorders (Ouellette *et al.* 1977) in the neonate and preterm birth (Miyake *et al.* 2014). It is well known that alcohol consumption alters the gut microbial composition (Dubinkina *et al.* 2017) even during pregnancy (Labrecque *et al.* 2016). These changes in the maternal gut microbial composition can affect the initial infant gut colonization, making it more prone to infections and diseases later in life. All in all, these studies emphasize that the maternal diet during pregnancy strongly influences the infant gut microbiota development.

### 2.2 *Maternal health during pregnancy*

Mothers share their microbes and metabolites with the foetus *in utero*, during delivery and lactation, and thus the maternal health during pregnancy affects the development of the foetus. The commensal microbial community in the human gastrointestinal tract plays crucial roles in the immune response and metabolic homeostasis, metabolic adaptations and, thus, in normal pregnancy (DiGiulio *et al.* 2015; Gomez-Arango *et al.* 2016; Smid *et al.* 2018).

Studies have shown that offspring of mothers suffering from any type of diabetes or having high BMI (overweight/obese) are at risk of developing diabetes and obesity in later life (Weiss *et al.* 2000; Whitaker 2004; Pirkola *et al.* 2010; Deierlein *et al.* 2011; Mehta *et al.* 2012; Gaillard *et al.* 2013). It is hypothesized that maternal diabetes and obesity influence the offspring's risk for developing chronic metabolic diseases, through changes in the maternal microbial composition during pregnancy and lactation (Singh *et al.* 2017). These alterations in microbial composition can have a negative impact on maternal and offspring health, by altering host metabolic pathways due to its effect on the abundance of genes that favour these metabolic pathways (Collado *et al.* 2010; Gaillard *et al.* 2013; Galley *et al.* 2014; Gallardo *et al.* 2015; Gohir *et al.* 2015; Hussen *et al.* 2015).

Direct studies trying to find the link between maternal health and infants have found that the microbial composition of infants born to obese mothers is distinct as compared to those born to lean mothers (Collado *et al.* 2010; Galley *et al.* 2014) and the offspring are associated with increased oxidative stress (Gallardo *et al.* 2015). Collado *et al.* analysed the gut microbial composition by fluorescent *in situ* hybridization with flow cytometry (FCM-FISH) and by quantitative real-time polymerase chain reaction (qPCR) in overweight and normal-weight pregnant women and observed that the infant's faecal microbial community was relatable to maternal weight gain during pregnancy. The authors found significant alterations in the gut microbial taxa in the two groups, of which *Bacteroides* and *Staphylococcus* were distinctly higher in overweight and obese women (Collado *et al.* 2008).

In another study, Collado *et al.* observed that high weight and BMI of mothers were associated with increased *Bacteroides*, *Clostridium* and *Staphylococcus* levels and decreased the abundance of the *Bifidobacterium* group. The presence of *Akkermansia muciniphila*, *Staphylococcus* and *Clostridium difficile* groups was decreased in infants born to mothers in the normal BMI range during pregnancy (Collado *et al.* 2010). Another study involved analysing the composition of the gut microbiota in 50 pregnant women in Spain by qPCR; they observed that Enterobacteriaceae*, Escherichia coli and Staphylococcus* numbers were increased, but *Bifidobacterium* and *Bacteroides* numbers were significantly reduced in overweight and obese pregnant women, which is contradictory with the previous study (Santacruz *et al.* 2010). Another study demonstrated that the microbiome associated with obese/overweight mothers leads to offspring with higher chances of obesity at early age. They reported that this can be extrapolated from the early life microbial composition of infants which can act as an indicator of obesity development in later life (Stanislawski *et al.* 2018).

Inflammation of the placenta and changes in feto-placental functions are seen as some of the adverse effects associated with maternal obesity or excess gestational weight gain (Challier *et al.* 2008; Kaphingst *et al.* 2008; Ditchfield *et al.* 2015). Though there is no definitive evidence supporting this hypothesis yet, new evidence from studies suggests that dysbiosis of the placental microbiota may be responsible for complications during pregnancy (Prince *et al.* 2016). The altered placental microbiome could be associated with ascending vaginal infections or oral commensal bacteria (Fardini *et al.* 2010). Out of the several factors that can affect the placental microbiota, gestational diabetes mellitus (GDM) is one. But only a few studies have investigated the effect of GDM on the placental microbiota (Bassols *et al.* 2016; Zheng *et al.* 2017). The authors in these studies confirmed the hypothesis that the placenta microbial composition in women diagnosed with GDM was different from that of normoglycaemic women. They observed a decrease in the abundance of the order *Pseudomonadales* and the genus *Acinetobacteria* in GDM women (Bassols *et al.* 2016) along with a rise in *Proteobacteria* levels, and a decrease in *Bacteroidetes* and *Firmicutes* in women with GDM (Zheng *et al.* 2017). Kumar *et al.* showed that neonates born to females with GDM are at high risk of developing atopic dermatitis and risk of allergen sensitization (Kumar *et al.* 2009), further associating GDM with childhood disorders.

To understand the effect of maternal diabetes on the microbiota of infants, a study analysed the meconium of neonate subjects born to mothers with diabetes before pregnancy and gestational diabetes and observed that their gut microbial composition grouped differently from those born to mothers without diabetes (Hu *et al.* 2013). Specifically, the meconium samples from the diabetes group had enriched levels of Bacteroidetes, members of the Lachnospiraceae family and Parabacteriodes genera, with lower levels of Proteobacteria. These alterations in the gut microbial composition were not affected by delivery mode, indicating the chances that maternal diabetic condition may have an impact on the foetal microbial composition, which in turn may affect the foetal health (Hu *et al.* 2013). It can be concluded from the above-mentioned studies that the main patterns seen in mothers suffering from obesity are high levels of *Bacteroides*, *Staphylococcus* and Enterobacteriaceae, with high levels of *Proteobacteria* and lower levels of *Acinetobacter*, *Bacteroides* and *Firmicutes* seen in mothers showing GDM. These changes predispose the offspring to higher chances of developing metabolic syndromes during childhood due to the dysbiotic microbial composition. Due to the higher chances of morbidity in offspring born to mothers with GDM or obesity, research is now focused on the effects of probiotics on pregnant women with GDM and obesity. Studies have shown that administration of probiotics to mothers with GDM results in better glycaemic control (Laitinen *et al.* 2009; Karamali *et al.* 2016), cholesterol levels, reduced insulin resistance and weight gain (Dolatkhah *et al.* 2015; Jafarnejad *et al.* 2016; Karamali *et al.* 2016) and reduced the risk of GDM (Laitinen *et al.* 2009; Luoto *et al.* 2010). Though there are studies which demonstrate no significant effects of probiotics during GDM and obesity in pregnancy (Lindsay *et al.* 2014, 2015; Zheng *et al.* 2018), none report any harmful effects.

It has also now been demonstrated by several studies that the baby *in utero* is not in a sterile environment and the amniotic fluid surrounding the foetus has its own unique microflora. Recent studies have observed higher microbial diversity and reduced alpha diversity in amniotic fluid samples associated with preterm deliveries (DiGiulio *et al.* 2008; Urushiyama *et al.* 2017). Another study by 16S rRNA gene sequencing identified *S. sanguinegens* and *F. nucleatum* in amniotic fluid as causes of preterm birth (Young-Ah *et al.* 2016). These studies indicate that maternal health during pregnancy must be closely monitored as any complications during pregnancy affect both the maternal and foetal health.

### 2.3 *Vaginal health*

The vaginal microbiome plays a possible role in the health of the mother and the newborn due to its direct contact with the foetus, and its possible role in colonizing the placenta. Vaginal dysbiosis during pregnancy is observed to be associated with negative reproductive outcomes, risk of postabortal infection (Larsson *et al.* 1992), early (Donders *et al.* 2000) and late miscarriage (Hay *et al.* 1994; Llahí-Camp *et al.* 1996) and premature rupture of foetal membrane and preterm birth (Hillier *et al.* 1995; Flynn *et al.* 1999; MacIntyre *et al.* 2015; Brown *et al.* 2018). The vaginal microbial composition of healthy mothers consists of members of the orders *Lactobacilliales*, *Clostridiales*, *Bacteroidales* and *Actinomycetales* (O'Hanlon *et al.* 2013).

To understand the role of vaginal health during pregnancy and its effect on infant health, Aagaard *et al.* studied the vaginal microbial composition of 24 healthy pregnant subjects. The authors observed that both richness and diversity were reduced during pregnancy with *Lactobacillus* being the dominant species observed (Aagaard *et al.* 2012). Romero *et al.* similarly reported the dominance of *Lactobacillus* spp. in healthy pregnant women in the first-ever longitudinal study of vaginal microbiota during pregnancy and also described increased stability of vaginal microbiota in pregnant woman compared to non-pregnant women of reproductive age (Romero *et al.* 2014). Similarly, Walther-António *et al.* studied the vaginal microbiota of 12 women during their healthy pregnancy at equal intervals of eight weeks in a longitudinal study and observed low microbiome diversity accompanied with high stability and dominance by *Lactobacillus* spp. (Walther-António *et al.* 2014). In another longitudinal study, MacIntyre *et al.* analysed the vaginal microbiota of 42 subjects during healthy pregnancy and the post-partum period. The authors reported that while the post-partum vaginal microbiome is not *Lactobacillus* dominant, it is more rich and diverse than the vaginal microbiota of ongoing pregnancies (MacIntyre *et al.* 2015). A study performed recently including 492 subjects confirmed the previous results and observed that the vaginal microbiome of women with healthy ongoing pregnancies has a relatively lower richness and diversity, along with a high abundance of *Lactobacillus* with a lower prevalence of *Mycoplasma* and *Ureaplasma*, which is otherwise related to preterm birth and low birthweight (Freitas *et al.* 2017), thus building our understanding of the vaginal microbiome in pregnancy. Other studies have suggested that the place of birth, that is either hospital or home, can also have an impact on the vaginal microbiota, which in turn can affect the infant gut microbial diversity which may last for long periods. They reported higher levels of *Clostridium* (Van Nimwegen *et al.* 2011; Combellick *et al.* 2018) and Enterobacteriaceae family (Combellick *et al.* 2018) in infants born in hospital as compared to those born at home. Nimwegen *et al.* reported that Vaginal home delivery was associated with a decreased risk of eczema, sensitization to food allergens and asthma (Van Nimwegen *et al.* 2011). Lactobacillus species (i.e., L. iners, L. crispatus, L. jensenii and L. gasseri) maintain vaginal health by maintaining a low pH and inhibiting the growth of pathogens (due to lactic acid production by fermentation of the available glycogen) and by producing a protein called bacteriocin that can actively kill unwanted bacteria (O'Hanlon *et al.* 2013). In a meta-analysis study, it was observed that bacterial vaginosis caused by the alteration in bacterial composition doubles the risk of preterm delivery and preterm labour, also predisposing the mother to higher chances of miscarriages and infection (Leitich and Kiss 2007). A large population-based study indicates that women with improper blood glucose levels have higher chances of vulvovaginal candidiasis infections as compared to those with controlled glucose levels (Faraji 2012; Sharma and Solanki 2014). Additionally, a few studies also report that the risk of vaginal mycoses in pregnant women with improper glucose levels is nearly two times higher (Nowakowska *et al.* 2004) compared to that in a pregnant woman with a controlled glucose level (Nowakowska *et al.* 2004; Lukic *et al.* 2017).

These studies indicate that the vaginal discharge during pregnancies (especially with GDM) must be checked for vaginosis and baseline data of the vaginal microbial composition and its abundance during pregnancy must be established to prevent pregnancy complications.

### 2.4 *Maternal exposure to antibiotics*

Exposure to antibiotic therapy and its modulatory effects on the human microbiome can begin *in utero* and continue throughout critical growth and development stages. Tanaka *et al.* 2009 demonstrated that alterations in the gut microbiota of infants whose mothers were treated with antibiotics were found to be similar to the alterations seen in infants treated with antibiotics, highlighting the influence of maternal medications on infant health (Tanaka *et al.* 2009). For example, it was observed in one of the previous studies that in mice, prenatal antibiotics reduces the diversity and structure of the microbiota in offspring (Tormo-Badia *et al.* 2014).

A recent study involving 36 overweight pregnant women studied the effect of the use of two intrapartum antibiotics Cephazolin and Benzylpenicillin by mothers on their infant's oral and gut microbial composition. They observed a high abundance of the family Streptococcaceae, Gemellaceae and Lactobacillales in infants born to mothers who were not exposed to intrapartum antibiotics. Along with this, families belonging to phylum *Proteobacteria* were found to be abundant in infants exposed to intrapartum antibiotics, a pattern often regarded as a signature of dysbiosis and inflammation (Gomez-Arango *et al.* 2017). Another study observed the effect of maternal antibiotic consumption on mothers and their nursing infant's gut microbiome. In this longitudinal study, breast milk and infant stool samples were collected at six time points from birth to one-month post-antibiotic initiation. It was reported that the relative richness of Bifidobacteria and Veillonella lowered after antibiotic treatment in most of the infant gut samples affecting the early colonizers of the infant gut (Rachel Rock *et al.* 2017).

A study by Gonzalez-Perez *et al.* 2016 demonstrated that in mothers treated with antibiotics during pregnancy and lactation, there were profound alterations in the composition of the gut microbiota in mothers and infants. *Streptococcus* spp. dominated the GIT microbiota of treated mothers, whereas *Enterococcus faecalis* predominated within the infant gut (Gonzalez-Perez *et al.* 2016). Another study demonstrated that the use of broad-spectrum antibiotics by pregnant mothers and infants at an early age can cause a shift in the gut microbial composition and may increase the

chances of development of colitis in susceptible offspring by affecting a critical stage of their microbial and immune development (Miyoshi *et al.* 2017). These findings point to the fact that uptake of antibiotics by mothers can affect the infant gut microbiome, which in turn can affect the infant's health and development and thus must be well observed and monitored.

## 3. Phase 2: Early infancy

### 3.1 *Mode of delivery*

The gut microbiome undergoes co-evolution with the host itself being influenced by various factors. The mode of delivery has a crucial impact on the type of microbiota ingested by the infant during birth. The delivery mode impact persists for months, and perhaps longer, after the birth as it contributes to microbiota development which can affect the normal physiological processes and disease development (Salminen *et al.* 2004; Dominguez-bello *et al.* 2010; Lorenza *et al.* 2014; Kumbhare *et al.* 2017). If a baby is normally delivered (vaginal delivery), the neonate comes in contact with the vaginal and the gut microbiome of the mother. The major microbiota colonizing the infant's gut is thus similar to the composition of the vaginal microbiome with a minor component being from the surrounding environment. On the other hand, a newborn delivered by caesarean section does not come in contact with the mother's vaginal microbiome, and the major component of the infant gut microbiome in this case is contributed by the nosocomial surrounding and the mother's skin microbiome. Recent studies reported a relatively increased risk of asthma (Chu *et al.* 2017b), obesity (Kuhle and Woolcott 2017; Rutayisire *et al.* 2016b), coeliac disease (Mårild *et al.* 2012) and type 1 diabetes (Cardwell *et al.* 2008; Adlercreutz *et al.* 2015) in children born via C-section, along with a lower frequency of atopic sensitization and allergy development in the vaginally delivered infants (Eggesbø *et al.* 2003; Negele *et al.* 2004; Bager *et al.* 2008; Huurre *et al.* 2008).

In particular, to determine whether the mode of delivery has an impact on the microbiome composition of the infant, researchers have studied the gut microbial diversity of infants from their birth to an age of 5–7 years as after this age an adult microbiome is established which remains throughout life. Earlier studies, such as those performed by Grolund in 1999, showed that the gut microbiome composition of infants delivered by caesarean delivery (CD) was significantly different when compared to vaginal delivery (VD) babies (Gronlund 1999). Vaginally delivered newborns exhibit bacterial taxa composed of various genera including Lactobacillus, Prevotella, Escherichia, Bacteroides, Bifidobacterium and Streptococcus spp. (Penders *et al.* 2006; Huurre *et al.* 2008; Dominguez-bello *et al.* 2010; Fallani *et al.* 2010; Azad *et al.* 2013; Liu *et al.* 2015). Another study by Biasucci *et al.* demonstrated that the gut microbiota of the caesarean delivery infants was less diverse than the microbiota of vaginally delivered infants, which may have long-term effects on the health of the infants (Biasucci *et al.* 2008), such as stronger immunological response (Huurre *et al.* 2008). In particular, it was demonstrated that CD delivered infants had minor amounts of *Bifidobacteria* (; Chen *et al.* 2007; Huurre *et al.* 2008; Dominguez-bello *et al.* 2010; Azad *et al.* 2013; Rutayisire et al. 2016a) and *Escherichia-Shigella* and absence of *Bacteroides* (Fallani *et al.* 2010; Song *et al.* 2013; Jakobsson *et al.* 2014), while VD delivered infants were characterized by *Bifidobacteria* (Hansen *et al.* 2015; Pandey *et al.* 2012), predominantly *B. longum* and *B. catenulatum* species (Gronlund 1999; Biasucci *et al.* 2008; Dogra *et al.* 2015) with higher amounts of *Klebsiella* in CD delivered infants (Dogra *et al.* 2015). Chu *et al.* 2017a, b and Dominguez-bello *et al.* 2010 showed that the differences in the intestinal gut microbiota of neonates were significant and seemed to be driven by the mode of delivery, demonstrating an increased association of *Propionibacterium*, *Corynebacterium* and *Streptococcus* with caesarean-born neonates resembling the skin surface microbiota, whereas *Lactobacillus* and *Prevotella* were observed to be associated with vaginally delivered neonates, which was more similar to their mother's vaginal microbiota.

It is also demonstrated that the mode of delivery and feeding habits have combined effects on the infant's gut microbiome (Song *et al.* 2013). It was found that *Bifidobacteria*, which is the dominant bacteria in VD delivered infants, has several beneficial effects for the infant's health, the growth of which in turn is affected by several stimulating factors present in human milk (Sela *et al.* 2008; Thurl *et al.* 2010). It is generally observed that caesarean section born infants have delayed colonization of *Bifidobacteria* and *Bacteroides* with over-representation of *Clostridium* and *Staphylococcus* and the Enterobacteriaceae family. To overcome this dysbiotic state and mimic the flora of vaginal birth infants in caesarean section infants, a new technique called vaginal swab seeding was introduced. The technique involves modulating the microbiota of caesarean section infants by swabbing the infants with mother's vaginal microbiome during birth. The first paper published by Dominguez-Bello and colleagues on vaginal seeding demonstrated that such swabs could restore the microbial composition of caesarean born infants, though partially, in a manner which was similar to the vaginal infant's microbiome (Dominguez-bello *et al.* 2016). This approach may not help to restore the exact microbial composition but will help in increasing microbial diversity and reduce the risk of immune-related disorders, but more studies on larger cohorts and longitudinal follow-up for longer durations are required to confirm the benefits.

3.1.1 *The preterm and full-term birth:* The pattern of gut microbial colonization in premature infants in an intensive care setting varies when compared with that of healthy, term and breastfed infants (Penders *et al.* 2006; Arboleya *et al.*

2012; Hill *et al.* 2017; Itani *et al.* 2017). Preterm infants (usually having very low birthweight) are at a downside in case of harbouring a well-developed set of gut microbiota. These observations can be attributed to several factors such as mode of delivery (mostly caesarean section). Thus, they never come in contact with the vaginal microbiome of the mother; another reason is the very low birthweight of the infants, which calls for special care to be taken, as a result of which they are usually not breastfed and are fed by other sterile means parenterally, with delayed complete nutritional feeding.

Furthermore, preterm infants are at a higher risk of infections due to living in an intensive care unit with a high bacterial load and frequent exposure to antibiotics, along with a delay in exposure to mother's skin and breast milk microbiome. These factors are together responsible for the reduced gut microbial diversity in preterm infants with increased colonization by pathogenic microorganisms.

In preterm infants with a gestational age of <33 weeks, the intestinal microbiota had reduced bacterial diversity (Gewolb *et al.* 1999; Rougé *et al.* 2010; Moles *et al.* 2013). Arboleya *et al.* (Arboleya *et al.* 2012) studied the gut microbial colonization in preterm and full-term infants and reported that preterm infants showed high levels of facultative anaerobes such as *Enterococcus*, *Enterobacter* and *Lactobacillus*, and lower levels of strict anaerobes like *Bifidobacterium, Bacteroides* and *Atopobium* when compared with term infants (Schwiertz *et al.* 2003; Magne *et al.* 2006; Arboleya *et al.* 2012). These results were similar to those reported by Magne *et al.* 2006 and Schwiertz *et al.* 2003 also reported higher levels of *Enterococcus*, *Staphylococcus* genera and the Enterobacteriaceae family. Also, it is observed that *Proteobacteria* and *Firmicutes* are among the phyla that dominate in PT infants when compared to FT infants (Embleton *et al.* 2017; Hill *et al.* 2017). Preterm infants thus show a perturbed early microbial composition compared to full-term infants, which increases their chances of developing immune system disorders, making them more prone to infections due to inadequate immune maturity linked to the dysbiotic microbiota.

### 3.2 *Feeding*

Human milk, mostly the first dietary exposure to the neonate, is the best link between the mother and the infant. It has a complex and dynamic composition which is very different when compared to the formula-based products in all aspects including nutritional value and its composition, such as the presence of certain growth factors and enzymes (Guaraldi and Salvatori 2012; Scholtens *et al.* 2012). These bioactive compounds (like human milk oligosaccharides), which are present in human milk, are beneficial to infants as they not only help better development but also strengthen the immune system of the newborn (Xiao *et al.* 2017), provide protection against allergies (Oddy 2017) and may also offer protection from coeliac disease (Akobeng 2005; de Palma *et al.* 2012), obesity (Miralles *et al.* 2006), type-2-diabetes (Pettitt and Knowler 1998; Pereira *et al.* 2014), diarrhoea (Strand *et al.* 2012) and many other metabolic disorders (Horta *et al.* 2007; Hoddinott *et al.* 2008; Walker 2010; Zivkovic *et al.* 2011). The WHO recommends that an infant must be breastfed for at least the first six months of life, following which introduction of solid foods should be done. Though a single component of breast milk does not influence the infant gut microbiota, there is evidence that human milk oligosaccharides (HMOs) play a significant role by stimulating the growth of *Bifidobacteria* and *Bacteroides* (Boehm and Moro 2008; Marcobal and Sonnenburg 2012). Human milk oligosaccharides modulate the health of infants by their actions such as prebiotic effect, modulating innate immune responses and intestinal cell responses and anti-inflammatory effects (Boehm and Moro 2008; Kuntz *et al.* 2008; Thurl *et al.* 2010). It is also demonstrated that human milk contains certain proteins and stimulation factors which enhance the growth of beneficial bacteria in the infant's gut which further help in the breakdown of complex oligosaccharides present in human milk (Thurl *et al.* 2010; Marcobal and Sonnenburg 2012).

To settle the question of whether the feeding habits have an impact on the gut microbial diversity of infants, many researchers have tried to study the faecal microbiota of infants fed with different feeding habits. Based on their study, Tannock demonstrated that there are differences in bacterial groups present in human milk and formula food (Tannock 1994). Cong *et al.* examined the relationship of feeding types and the infant gut microbiome; Breast milk feeding was found to be associated with a higher diversity of the infant's gut microbiome compared to non-breast milk feeding (Cong *et al.* 2016). Further, it has also been reported that in breastfed infants, *Bifidobacterium* species, specifically *B. breve*, *B. longum*, *B. dentium*, *B. infantis* and *B. pseudocatenulatum*, are the most prevalent *Actinobacteria* (Harmsen *et al.* 2000; Jost *et al.* 2012; Song *et al.* 2013; Bäckhed *et al.* 2015; Stewart *et al.* 2018). Also, *Firmicutes* phylum is constituted primarily of Lactic acid bacteria such as *Lactobacillus*, *Enterococcus* as well as *Clostridium* species (Harmsen *et al.* 2000; Bergström *et al.* 2014). Breastfed and vaginally delivered term infants show lower levels of C. difficile and E. coli and higher levels of Bifidobacterium spp., which are beneficial for infant health (Penders *et al.* 2006).

Based on the influence of feeding habits on the gut microbial composition of infants, a few studies are found to be contradictory and suggest that there are no significant differences in the bacterial composition of breast and formula-fed infants (Penders *et al.* 2006; Adlerberth and Wold 2009). However, most of the studies support the finding that *Clostridium* and the *Streptococcus* species, *Bacillus subtilis*, *Bacteroides*, *Escherichia coli* (Benno 1984; Fanaro *et al.* 2003; Penders *et al.* 2006; Adlerberth and Wold 2009; Fallani *et al.* 2010; Bergström *et al.* 2014; Timmerman *et al.*

2017) and *Enterococcus* (Fanaro *et al.* 2003; Adlerberth and Wold 2009), in the formula-fed infants were significantly higher than those in the breastfed infants. Further studies have shown that maternal health during lactation affects the milk microbiome. Since milk is a direct and major source of microbiome for the offspring, any changes in the milk microbiome can directly modulate the infant's gut microbiome which can have detrimental effects on the offspring's health. Milk from obese mothers has been found to contain a different and less diverse bacterial community compared with milk microbiota from normal-weight mothers (Cabrera-rubio 2012). It was observed that *Bifidobacterium* levels were reduced and those of *Staphylococcus* were increased in the milk samples of obese mothers as compared to the normal-weight mothers (Collado *et al.* 2012). Huurre and co-workers demonstrated lower levels of *Bifidobacterium* spp. in infants at an early age who were shown to mount a stronger humoral immune response, suggesting the vulnerability of the gut barrier (Huurre *et al.* 2008). Another recent study has demonstrated that feeding habits may interact with other factors such as child race/ethnicity to affect the infant gut microbial composition (Savage *et al.* 2018). Yet another study suggests that there is a complementarity relationship between breast milk composition and the associated microbiome, wherein bacteria producing specific amino acids present in reduced amounts in breast milk complement the composition, thus maintaining infant protein balance (Baumann-Dudenhoeffer *et al.* 2018).

### 3.3 *Use of antibiotics in neonates*

The use of antibiotics causes changes in the gut microbial composition by inhibiting the growth or killing of both beneficial and pathogenic species, thereby allowing the overgrowth of strains resistant to antibiotics, making the individual more susceptible to infections. These changes in the composition of gut microbiota caused by antibiotics can last for weeks to several months. The use of broad-spectrum prophylactic antibiotics in preterm or low birthweight infants is a very common practice. Because of the high susceptibility to infections in newborns with low birthweight/preterm and the difficulty in diagnosing infections in preterm infants, antibiotics are the most commonly prescribed class of medications in the neonatal intensive care unit (NICU) (Clark 2006; Patel *et al.* 2009). Consequently, this intervention reduces the diversity of gut flora (Fricke 2014) and delays the colonization of commensal flora and thus affects the host metabolic activity (Zhu *et al.* 2017). Of interest is the fact that studies have shown that the use of antibiotics and its prolonged exposure results in alterations in gut microbial ecology (Neu 2015; Cong *et al.* 2016), increased risk of inflammatory bowel disease in childhood (Hviid *et al.* 2011; Mårild *et al.* 2013) and can lead to antibiotic-associated diarrhoeas (AAD) due to nosocomial pathogens (Song *et al.* 2008). These negative outcomes are often associated with pathogens such as Klebsiella pneumoniae and Clostridium difficile (Young and Schmidt 2004; Song *et al.* 2008), which can lead to the development of Clostridium difficile associated diarrhoea (Beaugerie *et al.* 2003). Studies have also linked increased antibiotic exposure and decreased microbial diversity to increased risk for necrotizing enterocolitis (NEC) in premature infants (Alexander *et al.* 2011; Brower-Sinning *et al.* 2014; Hourigan *et al.* 2016). Gibson *et al.* observed the antibiotic resistome of premature infants in response to varying antibiotic exposures. They reported that the preterm gut microbiome has relatively reduced species richness; resistome analysis showed that meropenem, ticarcillin-clavulanate and cefotaxime treatments led to decreased species richness, while gentamicin and vancomycin had variable effects on species richness, highlighting the varying effects of antibiotic classes (Gibson *et al.* 2016). It was reported in another study that preterm infants who were exposed to antibiotic treatment for more than 5 days are associated with low bacterial diversity and an increased risk of sepsis (primarily caused by group B Streptococcus), necrotizing enterocolitis and death (Kuppala *et al.* 2011; Greenwood *et al.* 2014). Tanaka *et al.* 2009 and Fouhy *et al.* 2012 studied the microbiota of neonates treated with antibiotics in the early days of life and reported similar results. They observed that antibiotic exposure reduced the diversity of the infant's gut microbiota as well as altered its composition, with a decrease in levels of Bifidobacterium and rise in *Proteobacteria* levels. They observed that though the levels of gut flora bounced back by the study's end, the species diversity did not (Fouhy *et al.* 2012). Also, it has been observed that antibiotic resistance genes are present in infants at an age as early as two months, even though they were not subjected to antibiotic treatment (Zhang *et al.* 2011). Some possible reason for the same can be the vertical transmission of antibiotic-resistant organisms from the mother's milk, GIT or even from hospital environments where a high level of antimicrobial resistant organisms are observed (Leta *et al.* 2016), thus making the infant's gut a potential source of AMR genes. It is observed that antibiotic uptake during early life increases the risk of overweight and obesity in children in later life (Ajslev *et al.* 2011; Trasande *et al.* 2013; Bailey *et al.* 2018). Similar results about higher chances of adiposity due to early antibiotic exposure were reported by studies performed in mice models (Cho *et al.* 2012). Apart from obesity, the early use of antibiotics is also associated with increased risk of allergy development (Mckeever *et al.* 2002; Johnson *et al.* 2005). These studies suggest that the merits of administering broad-spectrum antibiotics in infants should be reassessed and other narrow-spectrum antibiotics must be sought for use for the shortest period possible.

## 4. Phase 3: Childhood

### 4.1 *Diet*

The beginning of weaning for infants marks the steady and slow approach of their gut microbial composition to that of

adults with some major shifts in taxonomic groups, and an increase in gut microbial diversity, thus pointing to the role diet plays in modulating the microbial community (Stark and Lee 1982; Koenig *et al.* 2011; Bäckhed *et al.* 2015; Stewart *et al.* 2018). Turnbaugh *et al.* performed experiments in germ-free mice by colonizing them with human microbial communities and observed that the bacterial community that colonizes initially is unstable and can be altered by diet even within a single day (Turnbaugh *et al.* 2009b). The introduction of solid food to the breastfed infant causes an increase in *Enterobacteria* and *Enterococci*, along with colonization by Bacteroides spp., Clostridium and Streptococcus. In contrast, formula-fed infants do not display such a sharp transition of gastrointestinal flora on the introduction of outside solid food (Stark and Lee 1982). This is because, since birth, formula-fed infants are exposed to a diet which includes certain complex compounds, thus establishing the microbial community to support the food habits.

The type of diet further affects the community structure of the gut microbiota. Carlotta De Filippo and colleagues analysed the faecal microbiota of European children (EU) and children from a rural African village consuming a western diet and a diet rich in fibre, respectively. They observed that children with the high fibre diet displayed a considerable increase in the *Bacteroidetes* level with a decrease in the level of *Firmicutes*. These results were accompanied by higher short-chain fatty acid levels in the rural diet of children than in the EU children with an abundance of a distinctive set of bacteria from the genus Prevotella and Xylanibacter, known to be responsible for fermenting cellulose and xylan to liberate energy (De Filippo *et al.* 2010).

Further, microbes in the distal gut contribute to host health through the biosynthesis of vitamins and essential amino acids, as well as the generation of important metabolic by-products from dietary components left undigested by the small intestine and producing SCFAs (Whitt and Demoss 1975; Walker *et al.* 1998; Metges *et al.* 1999; Magnúsdóttir *et al.* 2015). The type of SCFA and microbial species dominance depends majorly on the type of substrate available. For example, high levels of the *Bacteroidetes* phylum are seen in subjects consuming a high fibre and polysaccharide diet, while high levels of *Firmicutes* are seen in high-fat diet consumers (De Filippo *et al.* 2010; David *et al.* 2014; De Filippis *et al.* 2016). Changes in the gut microbial composition are also seen when the diet is switched from meat-based to a vegetarian diet (David *et al.* 2014; Gomez *et al.* 2016). It was reported that children consuming a more rural and less westernized diet had a gut microbial community structure that differed from those consuming a westernized diet. In a study that compared the gut microbiota of Bangladeshi and US children, it was observed that the Bangladeshi children who consumed a carbohydrate and rice-rich diet with bread and lentils and rarely any meat reported a dominance of *Prevotella* in these children when compared to the US children whose diet included animal meat and proteins, showing a dominance of Bacteroides (Lin *et al.* 2013). Another study reported that in children from Leyte, the occurrence of a particular type of microbial community was linked to a diet-dependent nutrient bias. In particular, the high-fat westernized diet of children from Ormoc was found to have association with a lower abundance of Prevotellaceae (P-type) microbiota, while the children from Baybay who consumed a carbohydrate-rich diet showed lower Bacteroidaceae and higher P-type microbiota, suggesting that the altered microbial composition could be a reason for obesity in children from Ormoc (Nakayama *et al.* 2017).

Bergstrom *et al.* assessed the faecal microbiota composition of 330 subjects and observed that changes in the gut microbiota occurred post weaning, from age 9 to 18 months; these changes include decrease in levels of *Lactobacilli*, *Bifidobacteria* and Enterobacteriaceae which dominate breast milk microbiota with an increase in *Clostridium* and *Bacteroides* spp. (Bergström *et al.* 2014).

The importance of the gut microbiome in the carbohydrate metabolism is seen in a case of dysbiosis caused by disruption of the mucous membrane, such as in the case of IBD or Crohn's disease, which results in a shift of the gut microbiome from obligatory aerobes to facultative aerobes and a reduction in the metabolism of carbohydrates to produce SCFAs, thus leading to intestinal inflammation (Morgan *et al.* 2012). Overall, shifts in the diet can modulate the bacterial composition which leads to the prevalence of microbes possessing genes responsible for the metabolism of various compounds (Gritz and Bhandari 2015).

### 4.2 *Exposure to antibiotics during childhood*

Antibiotic therapies worsen the situation by negatively influencing the already unstable gut microbiota in the subjects under medication. In addition, these alterations in microbial compositions can remain for long periods of time, spanning months and even years with partial or complete recovery (De La Cochetière *et al.* 2005; Huse *et al.* 2008; Dethlefsen and Relman 2011; Panda *et al.* 2014; Rashid *et al.* 2015). Use of broad-spectrum antibiotics allows growth of the pathogen *Clostridium difficile* which results in infections and severe diarrhoea (Stevens *et al.* 2011; Brown *et al.* 2013). Moran Yassour and colleagues investigated the effects of multiple antibiotic treatments in the first three years of life and found results very similar to those seen in adult studies. They measured the diversity and richness of the microbiota at the species and strains level and reported that antibiotic-treated children had less diverse and more unstable gut microbial composition compared to untreated children (Yassour *et al.* 2016). Another study on a cohort of 142 Finnish children aged 2–7 years reported that the use of macrolide was associated with enduring changes in microbial composition and reduced diversity. Certain variations, such as the abundance of *Bifidobacterium* and *Bacteroides*

and antibiotic resistance, were restored within a year after the antibiotic course. However, the abundances of certain other genera and diversity did not recover for about a couple of years after the course. Also, it was noted that penicillin use did not have as severe an influence on the microbiota, suggesting the varying influence of distinct antibiotics (Korpela *et al.* 2016).

Antibiotic resistance is a serious issue worldwide due to its effect on the resistome profile of the microbiome (Jernberg *et al.* 2007; Bengtsson-Palme *et al.* 2015), which is growing due to the ever-increasing use of antibiotics, as well as the slow-moving drug development due to economic and regulatory challenges (Piddock 2012). Multidrug-resistant (MDR) bacterial infections are rising rapidly in US children and causing longer hospital stays, according to a new study in the Journal of the Pediatric Infectious Diseases Society. In another study involving a culture-based method, the authors demonstrated that even healthy untreated children from various cities across three continents acted as reservoirs of multidrug-resistant genes, implying that healthy isolates from certain regions can also act as a source of MDR genes (Lester *et al.* 1990). A study in Bangladesh reported the increasing cases of MDR in children. Using a culture-based technique in 15 children, the authors observed that the gut of toddlers in Bangladesh acts as a reservoir for MDR bacteria of the family Enterobacteriaceae, with many bacteria containing plasmids with antibiotic resistance genes (Monira *et al.* 2017). Thus, it is now important to illustrate the ill effects of antibiotics abuse to prevent self-prescription and to spread awareness and implement the use of antibiotic stewardship programmes which will help curb the spread of antibiotic resistance in the population and reduce the spread of infections.

### 4.3 *Hygiene and microflora hypothesis*

In 1976, Gerrard *et al.* studied a relationship between the occurrence of allergy, atopic disease and stated, 'atopic disease is the price paid by some members of the white community for their relative freedom from diseases due to viruses, bacteria, and helminths' (Gerrard *et al.* 1976). Later, on similar lines, Strachan proposed the hygiene hypothesis suggesting that a lack of exposure to germs and infections, with an extremely clean environment during early childhood, may not be able to challenge the immune system enough to gain memory and be prepared for future infections, acting as a risk for developing childhood diseases. Strachan proposed that this inadequate development of the immune system in children may pose a threat to children's health by elevating the risk of allergies and other immune hypersensitivities in life. This exposure to a wide variety of germs in early life was linked to unhygienic contact with siblings or play areas (Strachan 1989). This theory was aided by the results of a study in a large cohort of children where the occurrence of hay fever was found to be inversely proportional to family size (Strachan *et al.* 1996). Since then, the theory has been supported by results from many studies stating that early-life exposure to germs through contact with pets or older siblings, as well as a larger family size, enhances the rate of maturation of the microbiome (Stewart *et al.* 2018) and acts as a shield against the risk of developing allergic disease and asthma (Ball *et al.* 2000). In contrast, certain studies suggest that exposure to cats, in particular, may lower the risk of allergic disease or asthma development but exposure to dogs may increase the risk (Takkouche *et al.* 2008), while some suggest the opposite (Hugg *et al.* 2008).

Gary Huffnagle proposes that the real reason for this relation between certain immune diseases and environmental pressure is that the western lifestyle limits microbial exposure to a great extent and thus modifies our gastrointestinal microflora, leading to establishment of tolerance, allergies and other inflammatory diseases, an idea called the 'microflora hypothesis' (Huffnagle and Noverr 2005). Bisgaard *et al.* studied children ($n$ = 411) at high risk of developing asthma and reported that reduced microbial richness was inversely related with the possibility of allergic sensitization, peripheral blood eosinophils and allergic rhinitis in the first few years of life (Bisgaard *et al.* 2011).

In another study, microbial diversity and composition were studied in children at the age of 2 from two different regions. It was observed that infants with allergic diseases had decreased levels of *Lactobacilli* and *Bacteroides* and higher levels of *Staphylococcus aureus* with higher proportions of aerobic microbes as compared to non-allergic children (Björkstén *et al.* 1999). Overall, it can be hypothesized that sequential changes in lifestyle can lead to changes in the gut microbial composition, which in turn can affect the maturation of the infant immune system and increase the risk of allergic disease development.

### 4.4 *Host genetics and gut microbiome during childhood*

Host genetic interactions act as a part of a complex network of factors affecting the microbial composition. The answer to how host genetics and environmental exposure modify the gut microbiota has been obtained through targeted and candidate gene approach studies.

Evidence for the influence of genetic make-up on microbial composition is provided by many studies reporting the link between the absence of FUT2 gene and alteration in gut microbial composition. The FUT2 gene encodes an enzyme α-1,2-fucosyltransferase responsible for the expression of ABO histo-blood-group antigens on mucosal surfaces (Kudo *et al.* 1996; Koda *et al.* 2000). Due to their enzyme secreting status, individuals who carry one or both the alleles are known as 'secretors,' whereas those possessing nonsense mutations without the enzyme are known as 'non-secretors'. Studies have reported that the Non-secretors are at a

disadvantage and are more prone to inflammatory disorders such as coeliac and Crohn's disease (McGovern *et al.* 2010; Forni *et al.* 2014), which may be possibly due to modifications in the gut microbiota (Rausch *et al.* 2011; Tong *et al.* 2014). In humans, twin pairs make it easier to study genotype changes and its health influences; thus, most of the studies providing such valuable information are based on twin pair studies.

Stewart and colleagues used temporal temperature gradient gel electrophoresis (TTGE) to understand the link between host genetics and microbial composition in children. While studying the Eubacterial population, the authors observed that the degree of similarity in the bacterial community was higher in identical compared with non-identical twins and was lowest in the unrelated control group (Stewart *et al.* 2005). Authors in another study further observed the role of several functional genomic variations linked to IBD in the genes NOD2, CARD9, ATG16L1, IRGM and FUT2. Analysis revealed that in healthy controls a higher genetic risk of IBD was associated with a decrease in the genus *Roseburia* of the phylum *Firmicutes* (Imhann *et al.* 2016).

In a recent study, Kumbhare *et al.* showed that the gut bacterial community structure in 13–14-year-old Indian and Finnish children differs significantly. Specifically, the Finnish children possessed higher Blautia and Bifidobacterium, while genera Prevotella and Megasphaera were predominant in the Indian children. The study also demonstrated a strong influence of FUT2 and birth mode variants on specific gut bacterial taxa, the influence of which was noticed to differ between the two populations under study (Kumbhare *et al.* 2017).

Apart from the studies performed in children, many studies have been performed in adults (Zoetendal *et al.* 2001; Turnbaugh *et al.* 2009a; Goodrich *et al.* 2014) involving gene targeted approaches which provide clear evidence that the host genetic make-up influences the gut microbial composition. Elaborate studies in human children are thus needed to provide a detailed understanding of the relationship between gut microbiota and host genotype from the initial stages; thus, it can act as a guide for microbiota targeted approaches.

## 5. Conclusion

A significant revolution in the sequencing technologies in the past decade has enabled researchers to decipher the 'host-microbe' interplay in a more robust and cost-effective way than earlier. This has enriched our understanding of the role of microbiota in human health and disease development, proving microbiota to be a major influencer of host health. The research studies discussed in this review have furthered our understanding of how the factors influence or are associated with immune and physiological development, the mechanisms of which are now known to be mediated through the microbiome. Thus, studies in this direction are needed to delineate the core microbial composition during early age and understand the role of the microbiome in host health development.

Understanding the changes in the gut microbial community right from the early stages may advance our knowledge of dysbiosis associated with the development of allergies, gastrointestinal diseases and metabolic disorders such as obesity and diabetes during childhood. These efforts will lead to the development of disease-specific biomarkers that can be used potentially for diagnostics and eventually to design treatment strategies.

Additionally, it is now evident from many studies that exploring the diversity of host-associated microbes will provide only a partial picture of the actual host-microbiome interactions; thus, use of multi-omics approaches will help us determine the functionality of these gut residents and provide deeper insights into the complex interactions. This integrated approach will eventually help in designing holistic treatment regimens, especially in the early stage of life, to improve both maternal and child health.

Considering the recent advancements in microbiome studies, the therapeutics for modulating the microbiome for health has now moved from being 'community medicine' to 'personalized medicine', thus posing a serious need to carry out comprehensive studies to understand the individual responses to the interventions carried out worldwide. These efforts will help in creating a personalized intervention, especially in mothers and infants, to modulate the microbiome and thus improve health.

It is to be noted that this review makes an attempt to summarize the current understanding based on the studies published till the time of constituting this article, and the authors sincerely apologize if not all the recent studies have been cited in this article.

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